REMARKS

Claims 22-25, 28, 29, 33-40, 43, 46, 47, 59, 62, 64, 87-89, 96, 101, 106, 108-111, 116, and 117 are pending. Claims 22 and 87 have been amended. The amendments to the claims do not introduce new subject matter and were made to more clearly define the claimed subject matter. The sensitivity limitations of claims 22 and 87 have been moved from the preamble into the body of the claim. A complete set of the pending (examined and withdrawn) claims is provided for the Examiner's convenience.

Attached hereto is a "VERSION WITH MARKINGS TO SHOW CHANGES MADE" to detail the amendments made to the claims.

Advisory Action

An Advisory Action was mailed by the Examiner on July 22, 2003. The Examiner indicated that the Amendment of May 28, 2003, would be entered but did not place the application in condition for allowance.

Specifically, the Examiner stated that the recitation of "at a sensitivity of one target cell per 100 or more total cells" was not given patentable weigh because the recitation was in the preamble. In response, the Applicants have now moved the sensitivity limitation into the body of the claims.

The Examiner further stated that the "Applicant has not shown that the claim limitations recited in the body of the claim would not result in the sensitivity recited in the preamble. The combination of Widder et al., Connelly et al. and Abram et al. encompass all elements in the recited claims. Therefore, it is the Examiner's position that the instantly recited claims are taught by the combined references." The Examiner appears to be making an inherency argument. However, Applicants point out that consideration of an inherent quality is relevant only to anticipation and not obviousness. *See Jones v. Hardy*, 230 USPQ 1021, 1025 (Fed. Cir. 1984).

As the outstanding rejections from the final Office Action of January 28, 2003, were not withdrawn, the following comments are made.

35 U.S.C. § 112 – Second Paragraph

In the final Office Action of January 28, 2003, claims 46-47, 106, and 117 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The applicants respectfully traverse this rejection.

While not conceding the correctness of the examiner's position, the applicants amended claims 46 and 117 in an Amendment filed May 28, 2003, obviating this rejection. Accordingly, the applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 103

Widder, Connelly, and Abram

Claims 22-25, 28-29, 33, 36-38, 59, 62, 64, 101, and 108-111 are rejected under 35 USC §103(a) over *Widder* et al. (EP 016,552) in view of *Connelly* et al. (U.S. Patent No. 5,422,277) in further view of *Abram* et al. (U.S. Patent No. 4,497,900). Applicants traverse this rejection and respectfully request reconsideration.

Widder discloses a method for coarse separation of blood cells through use of microspheres having protein A associated with the outer surfaces thereof. However, *Widder* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. *Connelly* does not overcome the deficiencies of *Widder*, as *Connelly* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. *Connelly* merely directs the reader to a cell fixative composition for fixing the internal components of a cell without disrupting the cell surface components.

Abram does not cure the deficiencies of *Widder* and *Connelly* and is further removed from the concept of the claimed invention. Instead of detecting a membrane structure on an intact, live target cell, the antibodies described by *Abram* are directed to antigens from lysed bacteria that have been absorbed onto plastic beads. Moreover, *Abram* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. Thus, the combination of *Widder, Connelly,* and *Abram* fails to teach all the elements of the claimed invention.

The office action states that the sensitivity levels claimed appear to be achieved by optimization procedures. However, the applicants assert that such a large difference in sensitivity as taught by the prior art in comparison to the sensitivity as claimed in the present invention cannot be a matter of mere optimization.

Widder discloses, for example, at the last line of page 11, that the non-specific binding is somewhat less than 10 percent. Based on this disclosed level of non-specific binding, one could not expect a sensitivity level of greater than 1 target cell per 10 total cells following the method of *Widder*. In contrast the present invention discloses and claims much greater sensitivity levels. Presently, the claims recite a sensitivity level of 1 target cell per 100 or more total cells. This represents a sensitivity that is at least one full order of magnitude greater. Further, the method of the present invention is capable of specificities even higher. A sensitivity of 1 target cell per 10^4 total cells is disclosed on lines 13-14 of the first paragraph on page 21. In view of the extreme differences in sensitivities between the prior art and the disclosed method, the applicants assert that such a difference cannot be achieved by mere optimization procedures.

Review of the case cited by the office action supports the view that the difference in sensitivities is not mere optimization. The office action cited Application of Aller, 220 F.2d 454, 456 (C.C.P.A. 1955) for the proposition that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." However, the present case is easily distinguishable from Aller. In Aller the only difference between the claimed invention and a SINGLE prior art reference was lower temperatures and higher sulphuric acid concentrations than in the reference. The court found that "the improvement is but a few percentage points different from the results reported by the reference." *Id.* at 457. In contrast, the difference in the sensitivities between the prior art and that claimed in the present case are a full order of magnitude different, or 1000%.

Therefore, *Widder*, *Connelly*, and *Abram*, taken alone or in combination, do not teach all the elements of the claimed invention. Applicants respectfully request this rejection be withdrawn.

Widder, Connelly, Abram, and Forrest

Claims 46-47, and 106 are rejected under 35 USC §103(a) over *Widder* et al. in view of *Connelly* et al., in further view of *Abram* et al. and *Forrest* et al. Applicants traverse this rejection and respectfully request reconsideration.

The Examiner maintains that it would have been obvious to incorporate the antibodies, buffers, beads, and reagents in the methods of *Widder, Connelly* and *Abram* into a test kit such as that taught by *Forrest* because test kits are conventional and well known in the art.

Forrest does not overcome the deficiencies of *Widder, Connelly* and *Abram*. As discussed above, the combination of *Widder, Connelly* and *Abram* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. *Forrest* does not teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. As such, a combination of *Widder, Connelly, Abram* and *Forrest* would not achieve the instant invention. Applicants respectfully request this rejection be withdrawn.

Widder, Connelly, Abram, Kemmner, and Holmes

Claims 34-35, 39-40, 43, 87-89, 96 and 116 are rejected under 35 USC §103(a) over *Widder* et al. in view of *Connelly* et al., and further in view of *Abram* et al., *Kemmer* et al. and *Holmes* et al. Applicants traverse this rejection and respectfully request reconsideration.

Kemmner and *Holmes* do not overcome the deficiencies of *Widder, Connelly* and *Abram*. As discussed above, the combination of *Widder, Connelly* and *Abram* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. *Kemmner* is cited for teaching isolation of tumor cells using magnetic beads coated with monoclonal antibodies. *Holmes* is cited for teaching a method of separating hematopoietic progenitor cells from a mixed population using microbeads coated with antibodies. However, *Kemmner* teaches their method as detecting only 40% of target cells present at a concentration of 73% of total cells (see page 199, second column). *Kemmner* teaches that steric hindrance and resulting reduced accessibility of epitopes for binding the antibody-coated beads, could be responsible for the reduced level of detection

as opposed to the better results obtained by immunofluorescent assay on frozen tissue sections. Thus, *Kemmner* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells.

Holmes is directed to separating blood cells from a blood or bone marrow sample, which is specifically excluded from the instant claims. Thus, *Holmes* cannot be seen to provide any guidance or motivation for modifying any of the previously described prior art to achieve the instant invention.

As such, the combination of *Widder, Connelly, Abram, Kemmner,* and *Holmes* fails to achieve the instant invention. Applicants respectfully request this rejection be withdrawn.

Widder, Connelly, Abram, Kemmner, and Forrest

Claim 117 is rejected under 35 USC §103(a) over *Widder* et al. in view of *Connelly* et al., in further view of *Abram* et al., and in further view of *Kemmner* et al. and *Forrest* et al. Applicants traverse this rejection and respectfully request reconsideration.

The Examiner maintains that it would have been obvious to incorporate the antibodies, buffers, beads, and reagents in the methods of *Widder, Connelly, Abram,* and *Kemmner* into a test kit arrangement such as that taught by *Forrest* because test kits are conventional and well known in the art.

Forrest does not overcome the deficiencies of *Widder, Connelly, Abram* and *Kemmner*. As discussed above, *Forrest* does not teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. As such, a combination of *Widder, Connelly, Abram, Kemmner* and *Forrest* would not achieve the instant invention. Applicants respectfully request this rejection be withdrawn.

35 U.S.C. § 112 – First Paragraph

Claims 22-25, 28-29, 33-40, 43, 59, 62, 64, 87-89, 96, 101, 108-111, 116, and 117 are rejected under 35 U.S.C. § 112, first paragraph, as not described in the specification. Specifically, the office action stated that the phrase "detecting a specific living target cell in a cell suspension of mixed cell population, or in a cell suspension prepared from a

solid tissue, at a sensitivity of one target cell per 100 or more total cells" is not supported in the specification. The applicants respectfully traverse this rejection.

Support for the sensitivity limitation of one target cell per 100 or more total cells is contained in the specification. The applicants draw the examiner's attention to Example 10 at page 22 of the specification where it is disclosed that tumor cells were detected using the method of the invention wherein the tumor cells comprised between 0.1 – 1 % of cells in the sample. This example provides support for the limitation of a sensitivity of one target cell per 100 or more total cells. The examiner's attention is further drawn to Example 8 at page 20 of the specification where it is disclosed that human breast carcinoma cells were detected at a sensitivity of one target-cell per 10^4 nucleated cells. This example also provides support for the limitation of a sensitivity of one target cell per 100 or more total cells. Finally, the examiner's attention is drawn to the paragraph beginning on line 8 of page 8. Here it is disclosed that the method of invention can be used to detect target cells which represent a very low fraction of the total number of cells (<= 1%). For at least these reasons the applicants assert that the limitation of one target cell per 100 or more total cells is clearly supported by the specification.

Support for the limitation of the cells being live cells is also clearly contained in the specification. The applicants draw the examiner's attention to the third paragraph on page 3 of the specification where it is disclosed that "the present method can be used for isolation of cells for biochemical, biological and immunological examination, and for studying of specific genes at the nucleotide or protein level, *in addition to culturing the cells*, without the need for cleaving the cell-particles complex." (emphasis added) The applicants submit that this clearly contemplates live cells because otherwise it would not be possible to culture the target cells after their isolation. Moreover, the method of the present invention clearly contemplates live cells because it is disclosed in the third paragraph of page 11 that the method can be used without fixatives such as formaldehyde or alcohols.

In sum, the phrase "detecting a specific living target cell in a cell suspension of mixed cell population, or in a cell suspension prepared from a solid tissue, at a sensitivity

of one target cell per 100 or more total cells" is clearly supported in the specification and the applicants respectfully request that this rejection be withdrawn.

In view of the remarks presented herein, Applicants respectfully submit that the claims are in condition for allowance. Notification to that effect is earnestly solicited. If prosecution of this case could be facilitated by a telephonic interview, the Examiner is encouraged to call the undersigned.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend claims 22 and 87 as follows:

22. (Five Times Amended) A method for detecting a specific living target cell in a cell suspension of a mixed cell population, in a fluid system containing a mixed cell population, or in a cell suspension prepared from a solid tissue[, at a sensitivity of one target cell per 100 or more total cells], with the exception of normal and malignant hematopoietic cells in blood and bone marrow, the method comprising the steps of:

a. coating paramagnetic particles or beads with a first antibody or antibody fragment directed against a second antibody or antibody fragment;

b. incubating the second antibody or antibody fragment with the cell suspension to bind the second antibody or antibody fragment with the target cell, thereby creating a cell mixture, wherein the second antibody or antibody fragment is directed against a membrane structure specifically expressed on the target cell and not on a non-target cell in the cell mixture;

c. washing the cell mixture to remove unbound second antibody or antibody fragment;

d. mixing the coated paramagnetic particles or beads with the washed cell mixture;

e. incubating the washed cell mixture and the coated paramagnetic particles under gentle rotation at about 4°C until target cell-bead rosettes are formed; and

g. visually detecting the target cell-bead rosettes after incubation;

wherein the target cells are living and can be detected at a sensitivity of one target cell per 100 or more total cells.

87. (Four Times Amended) A method for detecting living tumor cells in a cell suspension of mixed cell population or in a cell suspension prepared from a solid tissue[, at a sensitivity of one target cell per 100 or more total cells], with the exception of normal and malignant hematopoietic cells in blood and bone marrow, comprising:

a) coating paramagnetic particles with a first antibody or fragment directed against a second tumor-specific monoclonal antibody or fragment;

b) incubating the second tumor specific antibody or antibody fragment with the cell suspension to allow the second tumor specific antibody or antibody fragment to bind the tumor cells;

c) washing the cell suspension to remove unbound second antibody or antibody fragment;

d) mixing the coated paramagnetic particles with the cell suspension;

e) incubating the mixture at about 4°C under gentle rotation until tumor cell-bead rosettes are formed; and

f) visually detecting the tumor cell-bead rosettes;

wherein the target cells are living and can be detected at a sensitivity of one target cell per 100 or more total cells.